Remarks

Claims 1-16 are pending in the application. Claims 1-16 have been amended. New claims 17-20 have been added, supported at page 6 lines 6-8. No new matter has been added.

Applicant wishes to thank Examiner Carlson for her thorough review of the application. Applicant is in receipt of a non-final Office Action mailed July 29, 2005. In this Office Action, the Examiner indicated December 12, 2002 as the priority date of the pending claims. However, the correct priority date is December 2, 2002. The specification has been amended to reflect the priority date as requested by the Examiner.

RESPONSE TO INFORMALITIES IN THE DISCLOSURE

Amendments to the specification are made herein to address the Examiner's objections to informalities pointed out in the Office Action. Applicant believes all informalities have been addressed and respectfully requests that the objections be withdrawn.

The Applicant is submitting a new sequence listing and computer readable form (CFR) that includes the additional sequences that had been disclosed in the specification.

The Examiner posed a question regarding Applicant's intention to write the specification examples in a "prophetic manner" based on the verb tense used by Applicant. Applicant believes the specification and examples provide a written description that sufficiently teaches one of ordinary skill in the art how to make and use the invention in the verb tense that has been used. At least some of the steps in the examples, and the data presented in the examples, were actually performed (see, Ji, Yong et al., "Targeted Inhibition of Ca^{2+}/Calmodulin-dependent Protein Kinase II in Cardiac Longitudinal Sarcoplasmic Reticulum Results in Decreased Phospholamban Phophorylation at Threonine 17*", published July 4, 2003, The Journal of Biological Chemistry, the disclosure of which is co-authored by the Applicant). While use of the past tense in the patent example suggests that the work was actually done, there is no presumption that the use of the present tense is "prophetic" when actual data is presented.

Applicant also advises the Examiner that the above-mentioned Ji article, as well as the Kimura references, has been submitted in a supplemental IDS submitted on October 25, 2005. A copy of the Form 1440 is attached.

RESPONSE TO REJECTION UNDER 35 USC 101

Claims 1-16 have been rejected under 35 USC 101 as being directed to non-statutory subject matter. Applicant has amended claims 1-16 to provide for "An isolated polypeptide" and "An isolated nucleic acid". Applicant believes these amendments overcome the rejection under 35 USC 101, and respectfully requests that this rejection be withdrawn.

RESPONSE TO REJECTIONS UNDER 35 USC 112 SECOND PARAGRAPH

Applicant has amended claims 1-16 to include amino acid designations consistent with the instant sequence listing. Specifically, the numbering of the amino acids in the claims now corresponds to the sequence listing numbering of amino acids rather than that of native phospholamban. Furthermore, the specification has been amended to include sequence listing amino acid designations that correspond to the phospholamban designations so there is concordance between the "literature" numbering and the instant sequence listing numbering. No new matter was introduced by including this concordance. Applicant respectfully requests that this rejection be withdrawn.

Amended claims 1-16 contain the language "An isolated polypeptide" or "An isolated nucleic acid" where necessary to overcome the rejection under 35 USC 101. Applicant believes this claim language also addresses the examiner's rejection under 35 USC 112, second paragraph. Applicant respectfully requests that this rejection be withdrawn.

Claim 10 has been amended to depend from Claim 8.

Regarding amended claims 15 and 16, the language "or wherein the nucleotide sequence is linked to a compliment of a second nucleotide sequence encoding a protein to be targeted to a sarco(endo)plasmic region of a cell" has been added to claim 16 to address the Examiner's rejection under 35 USC 112, second paragraph (directed to cancelled claim 15)

regarding the antisense orientation of SEQ ID NOS: 4 and 6. Support can be found in page 8 lines 5-8. Applicant respectfully requests that this rejection be withdrawn.

RESPONSE TO REJECTIONS UNDER 35 USC 112, FIRST PARAGRAPH

The Examiner's rejects claims 1-3, 5, 6, and 11-14 under 35 USC 112, first paragraph, concluding that the specification does not describe how to make and use the invention commensurate with the scope of the claims. In particular, the Examiner cites that Kimura et al. (1997) shows a Val49Ala mutation results in loss of function of PLN, while Haghighi (2001) shows a Val49Gly mutation results in gain of function for PLN, wherein the identity of the amino acid substitution appears to determine the activity of PLN.

Applicant respectfully traverses with the Examiner's rejection. First, the Applicant's claims do not require or recite any "PLN function". The disclosed and claimed modified phospholamban transmembrane domains provide localization signals as described in the detailed description of the invention. While an embodiment can include a localization signal that does not disrupt other cell processes, the claims do not require such a limitation. Applicant believes that the Examiner may be reading unnecessarily into the claimed invention a problem associated with the prior art. The Examiner's reliance on a determination by one of ordinary skill of the activity of each mutated amino acid, as the basis for finding that the specification lacks guidance, lacks working examples, and requires an unreasonable quantity of experimentation is necessary, is manufactured and unfounded.

Second, Applicant's invention relates to making and using localization signals, which the specification teaches to one skilled in the art how to make and use. The practice of synthesizing polypeptides and/or modifying nucleic acid sequences is commonplace in the art. One ordinarily skilled in the art is familiar with modifying any amino acid to alanine as well as modifying to any other amino acid. The techniques employed in modifying to the amino acid of interest are standard repertoire. Applicant therefore believes that the invention as claimed is described and enabled according to 35 USC 112, first paragraph. Applicant respectfully requests that this rejection be withdrawn.

RESPONSE TO REJECTIONS UNDER 35 USC 102

Claims 1-3 and 11-13 have been rejected under 35 USC 102(b). Amended Claims 1 and 11, to which the remaining rejected claims depend, now recite at least two amino acid or codon substitutions, at the following positions in SEQ ID NO:1: Leu-9, Asn-12, Phe-13, Ile-16, Leu-20, Ile-26, Val-27, and Leu-30. Kimura et al. (1997 J. Biol. Chem. 272:15061-64) do not disclose or suggest two or more amino acid substitutions at the specific positions claimed. Since Kimura et al. do not disclose every element of the invention as claimed, this reference cannot anticipate Applicant's claims. Applicant respectfully requests that this rejection be withdrawn.

RESPONSE TO REJECTIONS UNDER 35 USC 103

Claims 1, 5, 6, 11 and 14 have been rejected under 35 USC 103(a) as being unpatentable over Kimura (1997) in view of Kimura (1996). Applicants respectfully traverse the rejection in view of the claim amendments, and request that the rejection be withdrawn. Claims 1, 5, 6, 11 and 14 have been amended, or depend to a claim that has been amended, to provide for two mutations. Furthermore, claims 5, 6 and 14 each recite linkage to a "compound" or "macromolecule" or "protein" that is to be targeted to a sarco(endo) plasmic region of a cell.

Kimura (1996) disclose adding an epitope to PLN so that the fusion protein can be detected, and provides only motivation for adding an epitope in order to analytically detect the fusion protein can be isolated and detected. Kimura (1997) disclose a double mutation, to demonstrate that a particular loss-of-function mutation dominated over a particular "gain-in-function" mutation, to result in an inactive PLN. Applicant contends that the Examiner can not make a prima facie case of obviousness against the amended claims, and can not point to any motivation in Kimura (1997) to provide other double mutations, or to any motivation in Kimura (1997) to add a detection epitope as disclosed in Kimura (1996), let alone a compound or macromolecule that is to be targeted to a sarco(endo)plasmic region of a cell, as provided in claims 5, 6, and 14.

Claims 1, 4, 8 and 15 have been rejected under 35 USC 103(a) as being unpatentable over Kimura (1997) alone. Applicant has amended claim 1 to recite at least two amino acid or

codon substitutions. The examiner argues that because Kimura (1997) teaches specific double mutants at positions 34 and 40 (of PLN) and at positions 35 and 44 (of PLN), respectively; that a double mutant at positions 31 and 34 (corresponding to positions 9 and 12 of this application) would have been obvious to one of ordinary skill in the art. Applicant submits the Examiner has presented an improper "obvious to try argument." First, Kimura (1997) demonstrated that the particular double mutation resulted in an inactive PLN. His motivation for forming the double mutation was to evaluate a "loss-in-function" mutation against a "gain-in-function" mutation. There is suggestion or motivation within Kimura (1997) that leads one of ordinary skill in the art directly to look at any other double mutations, including the particular double mutants that are claimed by Applicant.

Additionally, Applicant submits the Examiner has applied improper hindsight in rejecting claims under 35 USC 103(a) and has used the claims as a roadmap to read Kimura (1997) with insights taught by the Applicant's specification and not by Kimura (1997) itself.

Claims 7, 9, 10 and 16 have been rejected under 35 USC 103(a) as being unpatentable over Kimura (1997) in view of Kimura (1996). Kimura (1996) disclose adding an epitope to PLN so that the fusion protein can be detected, and provides only motivation for adding an epitope in order to analytically detect the fusion protein can be isolated and detected. Kimura (1997) disclose a double mutation, to demonstrate that a particular loss-of-function mutation dominated over a particular "gain-in-function" mutation, to result in an inactive PLN. Applicant contends that the Examiner can not make a prima facie case of obviousness against the amended claims, and can not point to any motivation in Kimura (1997) to provide other double mutations, or to any motivation in Kimura (1997) to add a detection epitope as disclosed in Kimura (1996), let alone a macromolecule, compound, or protein that is to be targeted to a sarco(endo)plasmic region of a cell, as provided in claims 7, 9, 10, and 16.

Finally, Applicant asserts that new claims 17-20 are neither disclosed or suggested by the prior art of record, including Kimura (1997) and Kimura (1996). Independent claim 17 is based on the isolated peptide sequence of claim 1 as filed, for use as a localization signal.

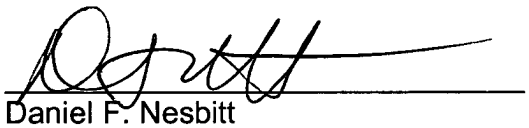
The use of a mutated sequence of the Kimura, and its function, as a localization signal to the sarco(endo)plasmic region of a cell is neither disclosed nor suggested.

CONCLUSION

Applicant believes that this provides a complete response to the Examiner's action. For the reasons set forth above, amended claims 1-16 and new claims 17-20 are believed patentable. Applicant requests withdrawal of all rejections and issuance of claims 1-20.

Applicant would appreciate a telephone call should the Examiner have any questions or comments with respect to this response. The Applicant is also eager to discuss the allowance of claims with the Examiner at the Examiner's convenience.

Respectfully submitted,

By: 

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